CRISPR-Cas9 Gene Editing of Hematopoietic Stem Cells from Patients with Friedreich's Ataxia.

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Public Summary:
Friedreich's ataxia (FRDA) is an autosomal recessive neurodegenerative disorder caused by expansion of GAA repeats in intron 1 of the frataxin (FXN) gene, leading to significant decreased expression of frataxin, a mitochondrial iron-binding protein. We previously reported that syngeneic hematopoietic stem and progenitor cell (HSPC) transplantation prevented neurodegeneration in the FRDA mouse model YG8R. We showed that the mechanism of rescue was mediated by the transfer of the functional frataxin from HSPC-derived microglia/macrophage cells to neurons/myocytes. In this study, we report the first step toward an autologous HSPC transplantation using the CRISPR-Cas9 system for FRDA. We first identified a pair of CRISPR RNAs (crRNAs) that efficiently removes the GAA expansions in human FRDA lymphoblasts, restoring the non-pathologic level of frataxin expression and normalizing mitochondrial activity. We also optimized the gene-editing approach in HSPCs isolated from healthy and FRDA patients' peripheral blood and demonstrated normal hematopoiesis of gene-edited cells in vitro and in vivo. The procedure did not induce cellular toxic effect or major off-target events, but a p53-mediated cell proliferation delay was observed in the gene-edited cells. This study provides the foundation for the clinical translation of autologous transplantation of gene-corrected HSPCs for FRDA.

Scientific Abstract:
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